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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/526,697
Filing Date: May 05, 2005
Appellant(s): DUDLEY ET AL.

Jeremy M Jay
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 12/22/09 appealing from the Office action mailed 12/17/08 .

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

US Patent 6,447,767

US Patent 5,126,132

WO 9705239

Dudley et al., J of Immunology,2001, v.24 pages 363-372

Riddell et al., J Immunol. Method, 1990, v.128, pages 189-201

Kawakami et al (PNAS, v.91, pages 6458-6462

Stevens et al., J of Immunology, 1995, v.154, pages 762-771

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Issue I

Claims 23- 35, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24,) or WO'9705239 each in view of US Patent 6,447,767 , Riddell et al. and US Patent 5,126,132

Dudley et al., teach a method of promoting the regression of melanoma in a mammal which comprising administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro (see entire document, Abstract and page 364 in particular). Dudley et al teach that to same patient IL-2 at various dosages (125,000 IU/kg -and 720,000IU/kg) was administered subsequently to autologous T cells (see Material and methods in particular). Dudley et al teach that some patient had also received the MART-1 peptide (see page 364 in particular). Dudley et al. teach that to overcome

the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including lymphodepleting chemotherapy. Dudley et al. teach that said treatment might improve lymphocyte survival and treatment efficacy.

WO' 239 teaches a method of promoting the regression of cancer in a mammal comprising administering to mammal an autologous T-cells which have been stimulated *in vitro* with antigen of the cancer (see entire document, Abstract and pages 12, 17, 22, 48 and 49 in particular). WO' 239 teaches the administration of IL-2 to the same patients at various concentrations (see pages 16 and 18 in particular)

The claimed invention differs from the reference teaching in that the Dudley et al., or WO' 239 does not explicitly teach a patient treatment protocol comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro and wherein said T cells which have been previously isolated and stimulated *in vitro* with the antigen of the cancer have been further subjected to one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2 .

US Patent '767 teaches a method of treating cancer patient, including melanoma, comprising administering to the patient non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering hematopoietic cells (see entire document, Abstract, columns 3, 4 , 8 and 9 in particular). US Patent '767 teaches that said non-myeloablative treatment should be used to overcome the poor persistence of adoptive transferred of T cells. Moreover, US '767 teaches that administering hematopoietic cells might contains T cells, since depletion T cell of donor stem cell has been know to increase the risk of graft rejection (see column 12 and 16 in particular). Thus, the examiner disagrees with applicant's statement, that " US Patent 767 only teaches administering non-myeloablative therapy prior to the administering hematopoietic stem cells , not T –cells" However, it is noted that said

statement is irrelevant for the instant rejection since US Patent'767 has been used as a secondary reference to show that at the time the invention was made one skill in the art would know that administering to the mammal nonmyeloablative lymphodepleting chemotherapy was a routinely used method to induced donor specific tolerance in a method of treating cancer patient, including melanoma.

US Patent' 132 teaches a method of treating cancer, including melanoma, comprising administering to the patient an effective amount of autologous tumor infiltrating lymphocytes (see entire document, Abstract in particular). US Patent'132 teaches a general methodology how to determine an effective amount of said cells and also teaches that the preferred amount is from about $5x\ 10^9$ to $5x\ 10^{11}$ cells.

Riddell et al., teach a method of *iv vitro* growing and expanding a large number of antigen specific T cells comprising rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. Riddell et al., teach an alternative culture method to clone and propagate human T cells that permitted retention of Ag specificity but did not require restimulation with Ag. Said expanded antigen-specific T cells would be useful for adoptive immunotherapy. IN other words, said reference has been used as the secondary reference to show that at the time the invention was made one skill in the art would know how to expand antigen specific T cells using irradiated allogeneic feeder cells, OKT3 antibody and IL-2.

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007).

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of US Patent '767, US Patent '132 and Riddell et al., to those of Dudley et al., or WO'239 to obtain a claimed method of promoting the regression of cancer in a mammal comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering an autologous T cell which have been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so, because to overcome the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering T cells as taught by US Patent '767 that can be used in combination with by the method taught by Dudley et al. or WO'239. The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

Claims 26 –34 are included because it would be conventional and within the skill of the art to : (i) determine the optimal duration and dosage of administering cyclophosphamide and fludarabine; or (ii) optimal amount of administered T cells. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Issue II

Claims 36, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24, IDS) or WO'9705239 in view of US Patent 6,447,767 (IDS), Us Patent 5,126,132 and Riddel et al., as applied to claims 23- 35, 37 and 38 above, and further in view of Kawakami et al (PNAS, 1994, V.91, pages 6458-6462) and Stevens et al (J. of Immunology, 1995, 154, pages 762-771)

The teaching of Dudley et al., WO' 239, US Patent '132 and US Patent'767 and Riddell et al., have been discussed, supra.

Dudley et al., WO' 625 and US Patent '767 and Riddel et al., do not explicitly teach a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100, as claimed in claims 36, 39 and 40.

Kawakami et al., teach melanoma differentiated antigens gp100 that is frequently observed as a targets of tumor infiltrating lymphocytes (see entire document, Abstract in particular). Kawakami et al., teach that peptides consisting amino acids 209-217 of gp100 has been used for in-vitro sensitization of T cells (see Materials and Methods in particular). Kawakami et al., teaches that incubation of T cells with said antigens consistently increase reactivity of T cells

towards said immunodominant epitope. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients

Stevens et al., teach melanoma differentiated antigens MART-1 that is frequently observed as a targets of tumor infiltrating lymphocytes (see entire document, Abstract in particular). Stevens et al., teach that peptides consisting of amino acids 25-35 of MART-1 has been used for in-vitro sensitization of T cells (see Materials and Methods in particular). Stevens et al., teach that incubation of T cells with said antigens consistently increase reactivity of T cells towards said immunodominant epitope. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the teaching of Kawakami et al., and Stevens et al., to those of Dudley et al., WO' 625 and US Patent '767 to obtain a claimed a method of promoting the regression of a cancer in a mammalian wherein antigen of cancer consists of amino acids 26-35 of MART-1 or amino acids 209-217 of gp100 with a reasonable expectation of success because the prior art teach the use of cancer antigen consisting of amino acids 25-35 of MART-1 or amino acids 209-217 of gp100 for in-vitro sensitization of T cells. Obtaining said melanoma-specific T cells would be beneficiary for treating and promoting regression of melanoma in patients

All the claimed elements were known in the prior art and one skill in the art could have combine the elements as claimed by known methods with no change in their respective function and the combination would have yield predictable results to one of ordinary skill in the art at the time of the invention (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007).

Specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involves not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art. See CTS Com. v. Electro Materials Corp. of America 202 USPQ 22 (DC SINY); and In re Burckel 201 USPQ 67 (CCPA).

From the combined teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Issue I

Claims 23- 35, 37 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24,) or WO'9705239 in view of US Patent 6,447,767 , Riddell et al. and US Patent 5,126,132.

At page 4 of the Brief, Appellant argues that there is no suggestion or motivation in prior art references to use only one cycle of rapid expansion of T cells for the claimed method of promoting the regression of cancer. Appellant further argues that Riddel et al., teach away from the claimed method, because Riddel et al., teach that successful adoptive immunotherapy requires large number of T -cells which are obtained through the use of repetitive stimulation with anti-CD3.

At page 6 of the Brief , Appellant indicated that as evidenced from Dudley Declaration, T cells in the prior art reference of Dudley et al (J of Immunology, May 2001, Vol. 24,) underwent multiple cycle of rapid expansion and that based on the poor objective clinical results obtained in Dudley et al., one skill in the art would not expected that T-cells that had undergone only one cycle of rapid expansion, as instantly claimed, would result in a positive, objective clinical response in patients. Appellant further indicated that as shown in the instant Specification and in Dudley Declaration, the method of Dudley et al (J of Immunology, May 2001, Vol. 24) use multiple cycle of rapid expansion and T cell fail to persist in the bloodstream of the patient and provide poor clinical result. In contrast, the claimed method, in which T-cell undergo only one cycle of rapid expansion, produce positive clinical result in this patient population and therefore succeed where other methods have fail.

At page 10 of the Brief, Appellant argues that contrary to expectation, administering T cells that had undergone only one round of rapid expansion, as claimed in the instant claims did unexpectedly produce superior, objective clinical responses in a patient.

As initial matter, it is noted that it has been recently stated that KSR forecloses the argument that a specific teaching, suggestion, or motivation are required to support a finding of obviousness See Board decision (see *KSR International Co v Teleflex Inc*., 550U.S.-, 82 USPQ2d 1385, 2007). The motivation need not be found in the references sought to be combined, but may be found in any number of sources, including common knowledge, the prior art as a whole, or the nature of the problem itself. In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999).

As explained in Motorola, Inc. v. Interdigital Tech. Corp., 121 F.3d 1461, 1472 (Fed. Cir. 1997), "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art."

Moreover, it is noted that Appellant mainly argues the prior art references individually not in their combination. In particular, the main arguments are based on the differences between multiple rounds of T cell expansion, taught in the primary reference of Dudley et al (J of Immunology, May 2001, Vol. 24) and one cycle of rapid expansion, as claimed in the instant claims.

Appellant failed to consider that the rejection of the instant claimed are based on a combination of primary and secondary references. There is not even discussion of the teaching of the secondary references of US Patent 6,447,767 and US Patent 5,126,132 in the instant Appeal Brief. However, the teaching of said references are critical for the instant rejection, since obviousness rejection under 35 U.S.C. 103(a) was based on combination of primary and secondary references.

The reason why "the claimed method, in which T-cell undergo only one cycle of rapid expansion, produce positive clinical result in this patient population and therefore succeed where other methods have fail" was that prior of administering T cells , **patients were treated with non-myeloablative chemotherapy.** In the methods taught the primary references said **non-myeloablative chemotherapy has not been used.** Said teaching, i.e. the use of nonmyeloablative treatment prior of administering T cell, are disclosed only in secondary references. Said references collectively teaches that **said non-myeloablative treatment should be used to overcome the poor persistence of adoptive transferred of T cells.** That's why, only in combination with the teaching of the secondary references, one skilled in the art would expect that T cells that were subject to only one cycle of rapid expansion of T cell would produced clinical response in patients.

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¶

Appellant, however, stated that " based the teaching Dudley et al (J of Immunology, May 2001, Vol. 24), " one skill in the art would not expect that T-cells that had undergone only one cycle of rapid expansion, would result in a positive, objective clinical response, and would logically attempt to improved the persistence and effectiveness of T cells by increasing the number of cycles of rapid expansion".
Said discussion failed to consider the teaching of the secondary references that the use of non-myeloablative chemotherapy treatment prior of administered of T cells will improved the persistence and effectiveness of administered T cells.

The instant rejection is under 35 USC103 and unobviousness cannot be established by attacking the references individually when the rejection is based on the combination of the references. see In re Keller, 642 F.2d 4B, 208 USPQ 871, 882 (CCPA 1981) See MPEP 2145. This applicant has not done, but rather argues the references individually and not their combination. One cannot show non-obviousness by attacking references individually where the rejections are based on a combination of references. In re Young 403 F.2d 759, 150 USPQ 725 (CCPA 1968).

With regards to Appellant's reliance on unexpected results over prior art method.

Appellant's reliance on unexpected superior results do not overcome clear and convincing evidence of obviousness. Also see Richardson-Vicks Inc. v. Upjohn Co., 44 USPQ2d 1181 (CAFC 1997). The issue is whether the properties differ to such an extent that the difference is really unexpected. As has been discussed supra, the main arguments for said "unexpected result" are based on the differences between multiple rounds of T cell expansion, taught in the primary reference of Dudley et al (J of Immunology, May 2001, Vol. 24) and one cycle of rapid expansion, as claimed in the instant claims. However, Appellant failed to considered that Dudley et al (J of Immunology, May 2001, Vol. 24) do not use non-myeloablative chemotherapy treatment prior of administered of T cells. Given the teachings of the secondary

references, that to overcome the poor persistence of adoptive transferred of T cells several variation on patient treatment protocol could be considered, including non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering T cells , one of ordinary skill in the art at the time of the invention was made would expect the combination therapy, i.e. non-myeloablative chemotherapy treatment prior to T cells administration, would result in a positive, objective clinical response , when T cell undergone only one cycle of rapid expansion.

The strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. In re Semaker. 217 USPQ 1, 5 - 6 (Fed. Cir. 1983). See MPEP 2144.

With regards to Appellant statement that "Riddel et al., teach away from the claimed method, because Riddel et al., teach that successful adoptive immunotherapy requires large number of T -cells which are obtained through the use of repetitive stimulation with anti-CD3".

A prior art reference may be considered to teach away when "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." In re Gurley , 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994). General skepticism of those in the art -- not amounting to teaching away -- is also "relevant and persuasive evidence" of nonobviousness. Gillette Co. v. S.C. Johnson & Son, Inc. , 919 F.2d 720, 726, 16 USPQ2d 1923, 1929 (Fed. Cir. 1990). In effect, "teaching away" is a more pointed and probative form of

skepticism expressed in the prior art. In any case, the presence of either of these indicia gives insight into the question of obviousness.

Riddell et al., teach a method of *iv vitro* growing and expanding a large number of antigen specific T cells comprising rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. The Examiner disagrees with Appellant's interpretation of Riddell et al., teaching. Riddell et al., teach an alternative culture method to clone and propagate human T cells that permitted retention of Ag specificity but did not require restimulation with Ag. Said expanded antigen-specific T cells would be useful for adoptive immunotherapy. However, nowhere do Riddell et al., teach that multiple rounds of rapid expansion should be used for adoptive immunotherapy. Moreover, it is noted that said reference has been used as the secondary reference to show that at the time the invention was made one skill in the art would know how to expand antigen specific T cells using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. There is no discouragement nor skepticism in Riddell et al., of using only one cycle of rapid expansion prior to adoptive immunotherapy, particularly in light of the fact that said reference does not used non-myeloablative treatment, including administering cyclophosphamide and fludarabine prior of administering T cells.

Issue II

Claims 36, 39 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dudley et al (J of Immunology, May 2001, Vol. 24, IDS) or WO'9705239 in view of US Patent 6,447,767 (IDS), Us Patent 5,126,132 and Riddel et al., as applied to claims 23- 35, 37 and 38 above, and further in view of Kawakami et al (PNAS, 1994, V.91, pages 6458-6462) and Stevens et al (J. of Immunology, 1995, 154, pages 762-771).

Given the absence of rebuttal to the outstanding rejections in Appellant's Brief, said rejection is maintained for the reasons discussed supra.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Michail A Belyavskyi/

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